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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,526	06/27/2001	Martin G. Crosby	UROMED-1	3190

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EXAMINER
PATTEN, PATRICIA A

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/27/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/891,526	Crosby et al.
Examiner	**Art Unit**
Patricia Patten	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 16, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5, 13-20, and 25-30* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5, 13-20, and 25-30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2, 16 and 18, drawn to a topical composition comprising borage seed oil and *Angelica pubescens* and *Coleus forskohlii* extract and a method for treating a sexual disorder with such a composition, classified in class 424, subclass 725 for example.

II. Claims 1 and 3, drawn to a topical composition comprising borage seed oil and vinpocetine, classified in class 424, subclass 422 for example.

III. Claims 1, 4, 5, 13, 14 and 15, drawn to a topical composition comprising borage seed oil, *Coleus forskohlii* extract and vinpocetine with an excipient, classified in class 930, subclass 250 for example.

IV. Claim 6, drawn to a composition comprising borage seed oil and *Coleus forskohlii* extract, classified in class 424, subclass 283 for example.

V. Claim 7, drawn to a composition comprising borage seed oil and vinpocetine, classified in class 508, subclass 472 for example.

VI. Claim 8, drawn to a composition comprising *Angelica pubescens* root and *Coleus forskohlii* extract, classified in class 514, subclass 906 for example.

VII. Claims 9 and 11, drawn to a topical composition comprising *Angelica pubescens* and vinpocetine or a composition comprising Angelica pubescens, vinpocetine and *Coleus forskohlii* extract classified in class 426, subclass 21 for example.

VIII. Claim 10, drawn to a composition comprising *Coleus forskohlii* extract and vinpocetine, classified in class 426, subclass 270 for example.

IX. Claims 12 and 17, drawn to a composition comprising borage seed oil, any angelica root species, *Coleus forskohlii* extract, vinpocetine, magnesium and ferulic acid, classified in class 252, subclass 380 for example.

X. Claims 19 and 20 drawn to a method for treating female sexual dysfunction via administration of borage seed oil classified in class 514, subclass 783 for example.

XI. Claim 21, drawn to a composition comprising GLA and osthole classified in class 514, subclass 547 for example.

XII. Claim 22, drawn to a composition comprising GLA and eburnamenine-14-carboxylic acid ethylester classified in class 514, subclass 558 for example.

XIII. Claim 23, drawn to a topical composition comprising osthole and eburnamenine-14- carboxylic acid ethylester classified in 548, subclass 573 for example.

XIIII. Claims 24 and 25, drawn to a composition comprising GLA, osthole and eburnamenine-14-carboxylic acid ethylester and a method for treating female sexual arousal with such a composition classified in class 514, subclass 943 for example.

The inventions are distinct, each from the other because of the following reasons

Groups I:II, I:III, I:V,I:VII, I:VIII, IV:VI, I:X, I:XI, I:XII, I:X:III, I:XIIII, X:XI, X:XII, X:XIII, X:XIIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions provide for different constituents which may provide for different effects when administered to an individual.

Inventions I:IV and I:VI and VI:VII and VI:VIII and VII:VIII are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because in each case, the subcombination recites '*Coleus forskohlii*' extract which could be any product obtained from any extraction. For example, forskolin, a phosphodiesterase inhibitor, is obtained via an alcohol extract of Coleus forskohlii. However, the ether extract provides for anti-bacterial substituents in the final product. The subcombination has separate utility such as an antibacterial agent for example.

The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Because these inventions are distinct for the reasons given above and the search required for each Group is not required for the others, restriction for examination purposes as indicated is proper.

During a telephone conversation with Anthony Zelano on 8/14/002 a provisional election was made with traverse to prosecute the invention of Group I, claims 1, 2, 16 and 18. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3-15, 17 and 19-25 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Amendment A received 8/16/02 has been entered. Claims 4, 6-12 and 21-24 were canceled. The remaining claims were amended to read on the Invention of Group I. Therefore, Claims 5, 13-20 and 25-30 were rejoined as belonging to Invention I and examined on the merits along with claims 1, 2, 16 and 18.

It is noted that in the Groupings on pp. 3-4 of the Amendment, claim 19 was not found in the groups. It appears that this was an inadvertent error. The correct groupings can be found *supra*. Further, Applicants argued the election with traverse in paper no. 6, arguing that an undue searching burden had not been established. However, as indicated by the separate classifications as set forth in the restriction requirement as described above, each respective group would necessarily need a

different divergent search of the subject matter. Since it appears that Applicants may have had incorrect groupings of the Inventions, the Examiner will not make this restriction final in this Office Action and will consider any arguments in a proceeding Amendment.

Claims 1-3, 5, 13-20 and 25-30 are pending in the application and were presented for examination on the merits.

Claim Objections

Claims 2-3, 5, 13-15, 26, 27, 28, 29 and 30 are objected to because of the following informalities:

All of these claims recite 'A topical composition of claim....'. It is suggested that the claim language be amended to read 'The topical composition of claim...' or alternatively 'A topical composition according to claim...' in order to clearly provide antecedent basis of the compositions in the preceding claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 16-18 are drawn to a method for treating sexual dysfunctions with compositions which do not comprise all of the constituents as outlined in Example 2 of the Instant Specification (i.e., including *Coleus forskohlii* extract containing 80% forskolin).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

In the Instant case, it has been demonstrated in the Instant specification that a mixture of ingredients which includes an extract of *Coleus forskohlii* was beneficial in treating sexual disorders relating to arousal and sexual response. However, Applicants

have not shown that any combination of the ingredients which did not contain the other constituents as outlined in Example 2 which included *Coleus forskohlii* extract actually worked.

The state of the art is unpredictable. Sexual disorders are widely prevalent, and treatments are scarce. Claims to treating sexual dysfunctions therefore need to provide clear evidence of such. Nowhere in the Instant specification is there any indication that any combination of the instantly claimed ingredients would actually work commensurate with the claimed invention except for the combination of elements which included *Coleus forskohlii* extract containing 80% forskolin, vinpocetine, Angelica pubescens root, borage seed oil and primrose oil (and inactive carriers). What other combinations of elements would produce the effects as set forth in the examples provided in the Instant specification? The skilled artisan would need to perform undue experimentation without expectation of success in order to evaluate the efficacy of other combinations of constituents which would be as pharmaceutically beneficial as the combination of the five ingredients above.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; ***however, he***

must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved." (emphasis added)

Claims 2, 3, 5, 13-15, 19, 20, 25, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods comprising an extract of *Coleus forskohlii* which contains 80% forskolin, does not reasonably provide enablement for *any* extract of *Coleus forskohlii*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Forman factors were outlined *supra*.

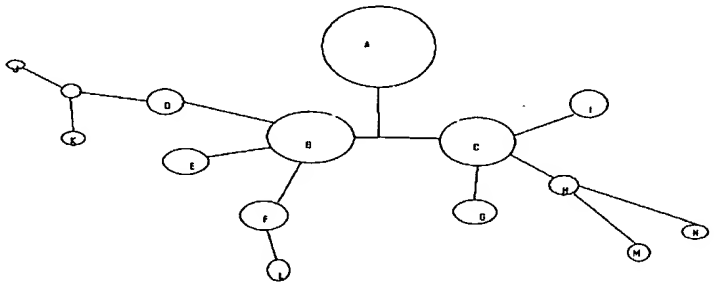
The art of phytochemistry is unpredictable with regard to plant extracts. Applicants use the term 'extract' broadly without defining exactly what extracts the claim encompass. Plants, and fruits and seeds thereof, are intricate living organisms which inherently possess an enormously diverse array of potential pharmacological ingredients. Just recently has the scientific community begun examining plants (as well as parts thereof) to evaluate their phytochemical constituents for medicinal purposes.

It is well known in the herbal art that polarity of solvents plays a key role in determining the final product obtained by an extraction. However, because many phytochemicals remain undiscovered, the skilled artisan has to make his best educated guess as to what types of phytochemicals will be successfully extracted with a solvent of a particular polarity. Often times, unless the constituents in a particular plant extract have been well evaluated and documented in the literature, the skilled artisan must adhere to trial and error protocols in order to quantitatively determine phytochemical constituents present in samples obtained from respective extraction procedures. These procedures are common when, for example, a plant or part thereof has been documented in the literature as possessing some medicinal quality. The skilled artisan will carry out numerous tedious extraction protocols in attempting to isolate the particular ingredient(s)

which has/have this medicinal quality. Typically, beginning with the first crude extraction, it is a guess as to whether or not the extract will possess the inherent medicinal quality. Take for example, the grape, *Vitis vinefera*. If this fruit was documented in the literature as having a particular medicinal qualities, the skilled artisan may feel the need to extract and isolate the medicinally beneficial ingredient(s) therefrom.

First, the skilled artisan would need to ascertain if the active ingredient(s) is/are found on the inside of the fruit; i.e., pulp or juice, or if alternatively, the active ingredient was found in the skin of the fruit. Thus, a first 'extract' may be obtained via pressing the fruit to obtain the juice and pulp of the fruit. The pulp and juice of the fruit would constitute a first product ('extract') with many various cell constituents. Of course, a determination would need to be made of if the extract, in this case, the pulp and the juice, actually possess the medicinal qualities as previously documented. If for example, the pulp and the juice of the grape did not prove to possess the documented medicinal quality, the skilled artisan would then test the skin of the grape for said quality (commonly, prior to solvent extraction, homogenization of the solids occurs via blending or vortexing). If the skin of the grape actually possessed the documented quality, the skilled artisan may then attempt to purify the ingredient(s) further. Then, the skilled artisan will, by trial and error, attempt to perform step-wise extractions to isolate the active ingredient(s).

If the first extraction attempt with a particular solvent fails, another solvent will be tried. Thus, beginning with the initial extraction, a first product is yielded which was extracted with the solvent, and a second product is yielded which remains



because it did not possess a similar polarity to the solvent.

Each successive extraction yields different products due to the exclusion of ingredients based on the polarity of the solvents solvating constituents with similar polarities. Subsequently, the properties of each respective product would need to be evaluated for efficacy.

Above is an illustrative example of the many products which may be produced by different successive extraction protocols.

In this example, assume that A= the initial water extract from a homogenized sample of grape. The water extract from the grape is then subjected to a methanol/water extraction to form products B (soluble with methanol) and C (more soluble with water). Product C is then extracted in a separatory funnel with three organic solvents: chloroform, benzene and ethyl ether to form products G, H and I which solvate with the respective solvents based on the polarity of the inherent constituents. Product H, which we will assume is the product obtained in the benzene fraction, is extracted again in a separatory funnel with benzene and methanol to remove any residual methanol-soluble constituents. The additional circles represent extractions which may be done to obtain different products, using similar solvents as discussed previously, or entirely different solvents. Consequently, the properties of each respective product would need to be evaluated for pharmacological efficacy. This representation is indicative of the vast array of distinct products which may be obtained due to the enormity of possible extraction permutations.

Additionally, according to the Stedman's dictionary 27th Ed, the term 'extract' means 'A concentrated preparation of a drug obtained by removing the active constituents of the drug with suitable solvents...'. Thus, purification of any

of these products in the illustrative example to yield a specific phytochemical would constitute an 'extract' judging from the definition provided by Stedman's Medical Dictionary. Therefore, resveratrol, a phytochemical inherent in grapes, is deemed to be an 'extract' of grapes since it is obtained by the process outlined in Stedman's. Therefore, each respective phytochemical found within grapes constitutes an extract once it is 'extracted' away from the rest of the grape's constituents. Here, the unpredictability with regard to the term 'extract' in the claims has grown exponentially.

Each product obtained from an extraction is unpredictable in nature. Even the most skilled of artisans would need to quantify each product for constituents as well as medicinal efficacy. Unpredictability with regard to plant extracts has been well documented in the art. Revilla et al. for example (1998) showed that the slightest variations in polarity of solvent and reaction time upon grape extraction, provided respective products with unique characteristic properties (See Tables 1, 2, 4, 5, 6 and 7). In turn, each product would possess varying pharmacological properties based upon their respective phytochemical constituents.

The preceding is evidence that the mere recitation of the term 'extract' does not provide the skilled artisan with the information needed to make the claimed invention. Accordingly, lacking information with regard to exactly what extract

Applicants intend, it would take undue trial and error experimentation without a reasonable expectation of success for the skilled artisan to make and/or use any extract of Coleus forskohlii besides the one clearly disclosed in the Instant specification for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 13-15, 19, 26, 27, 28, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Habif et al. (US 5,690,947) in view of Horrobin et al. (US 5,614,208), Oblong et al. (WO 00/69406), Kuniyoshi et al. (JP 405194179A-English Abstract) and Tian (CN 1104886A-Abstract). Claims 1-3, 5, 13-15, 19, 26, 27, 28, 29 and 30 are drawn to compositions comprising borage seed oil, Angelica root, vinpocetine, *Coleus forskohlii* extract, primrose oil and carriers.

Habif et al. (US 5,690,947) disclosed that borage seed oil was used topically on the skin to reduce skin irritation (col.2, lines 59-61).

Horrobin et al. (US 5,614,208) disclosed that primrose oil was known to be an active ingredient in skin care products (col.2, lines 35-38).

Oblong et al. (WO 00/69406) disclosed that forskolin, an extract of *Coleus forskohlii* was beneficial in healing keratinous tissue when administered topically (Abstract).

Kuniyoshi et al. (JP 405194179A-English Abstract) disclosed that vinpocetine, when applied topically, had a 'skin improving effect.'

Tian (CN 1104886A) disclosed that Angelica root was used in skin creams to beautify and heal dry skin (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for treating skin conditions and they are all used topically for this purpose. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves

synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore obvious.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him.

Although none of the references specifically recited the claimed carriers, all of the carriers as outlined in the claims were conventional carriers for topically administered formulations. Thus, one of ordinary skill in the art would have been motivated to have added carriers such as lecithin to emulsify the product in order to have created a cream form of the composition for example.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER R. TATE
PRIMARY EXAMINER